blood-sugar values, though the role they may play in alimentary hyperglycemia, which is pronounced in nephritis, I am at this time not prepared to say.

8. A rise in blood-sugar occurs in pneumonia and may be present in the absence of fever. It is apparently uninfluenced by blood-pressure, leukocytosis, or renal involvement.
9. Hyperglycemia occurs quite constantly in apoplexy, typhoid, and tuberculosis in the presence of fever and in some cases of cancer.
10. The test, owing to its simplicity and accuracy, affords a practical method for early diagnosis and control of dietary therapeusis.

I wish to express my appreciation of the kind assistance given by Dr. A. I. Ringer in the perfecting of the technique of this method and to Dr. Morris J. Lewis for the opportunity to study some of the pneumonia patients who were on his service in the Pennsylvania Hospital.

All the other cases were from the wards of the University Hospital on the service of Dr. Alfred Stengel.

EXTRAPHYSIOLOGICAL OR PUTREFACTIVE UREA.

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Schematically considered, the destruction of nitrogenous foodstuffs in the animal body end in the formation of the two principal and characteristic organic constituents of the urine, urea and uric acid. Neither, nevertheless, represent the last residue of the gradual disintegration of nitrogenous substances; they originate, on the contrary, through a synthetic process performed principally by the liver from ammonia, which may be considered as the most simple residue of the nitrogenous katabolism. In birds and reptiles the ammonia gives rise to uric acid, and in man and mammalians to urea. The small *proportion of uric acid found in the urine of the* latter proceeds from a real *process of gradual dissociation of nucleins.* These substances are disintegrated until xanthic bases result, which, by means of enzymatic oxidation, are turned into uric acid. While in birds and reptiles the introduced urea turns, in its greatest part, into uric acid, in mammalian animals certain enzymes which exist in various organs (Schittenhelm's uricolytic ferments) tend to destroy the uric acid, changing it into urea. Though apparently opposite it is probable that both compounds may proceed in each case from the same physiological process.

How does urea originate from ammonia? This is not entirely known, but the principal explanation of this biological fact is to be found in the Nencki-Schultze-Schmideberg anhydration theory and in the Hofmeister oxidation theory; both theories suppose the preëxistence of ammonia. It is not well fixed, at present, what part of the truth corresponds to each one of these theories. It is not known also if there are other organs besides the liver which may produce the urea from ammoniacal compounds. Especially interesting is the formation of urea from arginin; here, 50 per cent. of the nitrogen of this substance is directly dissociated by a ferment which has been isolated from the liver, kidneys, thymus, and other lymphatic glands.

The following conclusions can be accepted as well-established facts: (1) the urea proceeds in the body from ammoniacal compounds; (2) the liver is the only organ for which the formation of urea has been experimentally proved; (3) the urea may derivate also from dissociation of other nitrogenous compounds, as, for example, arginin.

Though all nitrogenous foodstuffs which are decomposed in a given animal do not give rise, however, to the production of urea, this principle may be considered as the main nitrogenous product of tissue katabolism, at least in man and mammalians, and therefore it is a substance entirely physiological to the animal body.

In the present article I will endeavor to expose the experimental basis upon which it is possible to establish that, in the common conditions of human life, a part of the urea, as small as it may be, proceeds directly from the intestinal putrefaction; that is to say, it is the product of chemical transformations which takes place outside of the normal tissue katabolism. This part of the urinary urea must receive the name of extraphysiological or *putrefactive* urea. In the sick man, especially in the diabetic, the putrefactive urea increases enormously and plays an essential part in the pathogeny of the malady.

If a solution of an ammoniacal salt of a volatile or inferior fatty acid is introduced into the rectum and its entire absorption permitted the result to be observed is that the twenty-four hours, amount of urea increases. This hyperexcretion of urea is accompanied by two interesting phenomena when butyrate of ammonia is the employed salt. The twenty-four hours' urinary volume increases (polyuria) and the excreted acetone greatly augments upon the normal proportions (acetonuria). If the rectal injections are continued for many days the polyuria and the acetonuria reach a high degree.

One of the experiments has been carried out on a subject specially selected in order that the pharmacological influence of the salt could reach the strongest effect with the least quantity used. The person referred to is a female, weighs 45 kilos, lives in the tropical and Atlantic region (Caracas, Venezuela), and is submitted to a uniform vegetarian diet very poor in nitrogen. The experiment has been divided into two series: the first series has been preceded by a preparatory period of the same diet. During the second series rectal injections of a watery solution of butyrate of ammonia have been used: 50 c.c. the first two days, 75 c.c. the two following, and 100 c.c. the rest of the series. The proportion of ammonia is exactly determined (3.825 grams NH_3 for 100 c.c.) and pure butyric acid (19.8 $C_4H_8O_2$ for 100 c.c.) is added until neutralization takes place; the rosolic acid has been employed as indicator. The daily quantity is diluted four or five times with water and fractionally injected. The quantitative estimation of the various urinary elements has been made as accurately as possible, employing the most reliable methods. The urinary volume has been determined by weight and density, the pipettes and flasks being graduated at the laboratory temperature (24° C.). For the quantitative estimation of the urea the slightly modified method of S. R. Benedict and F. Gephart[1] has been employed: The urine mixed to its own volume of diluted HCl (1 to 4) has been submitted in autoclave to a pressure of 6 atmospheres (150° to 155° C.), during one and a half hours. The resulting ammonia has been determined by the Krüger-Reich-Schittenhelm[2] method, and the preformed ammonia has been substracted. The uric acid has been estimated by the E. Wörner[3] method: the precipitated urate of ammonia dissolved into a watery solution of caustic soda is placed on a water bath to drive out the ammonia. The remaining nitrogen has been finally determined by the well-known Kjeldahl method. The acetone by the Huppert-Messinger[4] method, and on account of necessary comparative estimations for other purposes the volatile fatty acid has been evaluated by the Strauss-Philippsohn method. The obtained analytical results are condensed in the following table:[5]

FIRST SERIES. NORMAL CONDITION.

Days.	Volume. c.c.	NH_3 gm.	Total N. gm.	Urea. gm.	Uric acid. gm.	Acetone. mg.	Hepatic coefficient. per 100.
1st . . .	1235	0.610	6.003	9.687	0.345	7.0	75.0
2d . . .	1344	0.635	6.523	11.068	0.411	5.0	79.0
3d . . .	1255	0.476	6.036	10.629	0.361	8.0	77.0
4th . . .	1251	0.540	5.827	10.511	0.385	3.0	84.0
5th . . .	1460	0.613	6.428	11.443	0.415	3.0	82.0
6th . . .	1151	0.498	5.722	9.743	0.342	9.0	79.0
7th . . .	1422	0.541	6.645	10.772	0.388	5.0	75.0
Averages	1303	0.559	6.169	10.5501	0.378	5.7	78.7

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[1] Jour. of Am. Chem. Soc., xxx, 1760.

[2] Abderhalden, E., Physiologisches Praktikum, Berlin, 1912, p. 130.

[3] Hoppe-Seyler's Handbuch der physiol- und pathol- chemischen Analyse, Berlin, 1903, pp. 448-449.

[4] Strauss, H., and Philippsohn, H., Zeitschr. f. klin. Med., xi, 369.

[5] Delgado Palacios, G., Chimie pathologique tropicale de la région atlantique. Caracas. Lit. y Tip. del Comercio, pp. 219-293, 238, 103-125, 116.

SECOND SERIES. ACTION OF BUTYRATE OF AMMONIA.

Days.	Volume. c.c.	NH_3. gm.	Total N. gm.	Urea. gm.	Uric acid. gm.	Acetone. mg.	Hepatic coefficient. per 100.
1st . . .	1816	0.581	7.753	13.442	0.365	84	80.7
2d . . .	1858	0.411	8.122	14.989	0.410	108	85.9
3d . . .	1928	0.404	8.501	16.701	0.328	132	91.5
4th . . .	2304	0.405	8.533	17.344	0.321	149	94.7
5th . . .	2905	0.362	8.956	17.545	0.344	202	91.2
6th . . .	3044	0.392	9.008	18.042	0.309	235	93.3
7th . . .	2525	0.663	8.898	16.938	0.486	245	88.7
Averages	2340	0.4597	8.538	16.428	0.366	165	89.4

I have already pointed out why the physiologically produced urea in this person is so small, namely, an average of 10.5 gm. with a corresponding volume of 1300 c.c. The greatest excess of urea which has been synthetized by the liver, namely, 8 gm., has developed a very powerful diuretic action. It is interesting to note that this person with a total amount 18 gm. urea has excreted 3 liters of urine, which has the physical appearance of diabetic urine, while it is of common occurrence that the majority of persons with this quantity of urea do not excrete more than half a volume. In all my experiments with a starting physiological amount of urea double this one the butyrate of ammonia has had the same diuretic effect, but not so marked as in this case.

The diuretic action of urea is a constant experimental fact, and all the authors admit it. The increase of acetone or iodoform giving compounds upon the normal deserves, in this case, a closer exaplanation. All authors agree in accepting that the volatile fatty acids, when ingested under certain conditions, are completely oxidized in the body, except in case they contain some inorganic radicle. Otto Porges'[6] memoir on the subject may be quoted as a standard monograph upon the destruction of fatty acids in the organism. When butyrate of ammonia is ingested this salt is transformed into urea and butyrate of sodium, which is totally destroyed by oxidation in the body. If the same salt is absorbed through the rectal mucous membrane it arrives immediately at the liver, where the hepatic cell changes it into urea and butyric acid, with the production of a little quantity of acetone. This last transformation has been realized by G. Embden[7] and his collaborators when they made the artificial irrigation of the liver with blood containing substances capable of giving acetone (acetogenic substances), the butyric acid being the principal between them, and certain of its derivatives. The same production of acetone has been carried out on diabetics by making them ingest acetogenic compounds.

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[6] Ueber den Abbau der Fettsaüren im Organismus, Asher u. Spiro, Ergebnisse der Physiologie, 1910, p. 8.

[7] Hofmeister's Beiträge, 1904, vi, 59; Embden, G., and Karberlah, F., Hofmeister's Beiträge, 1906, xxx, 120; Embden, G., Salomon, H., and Schmidt, Fr., Hofmeister's Beiträge, viii, 129.

In this case the real interpretation of observed facts deserves a long explanation which space will not permit. Those interested in the subject may read the chapter Diabetic Pathogeny in a book I have published with the title *Tropical Pathological Chemistry* of the Atlantic region.[8]

From the experiment already referred to and others not quoted, easy to be conducted in man, we are right in concluding that the large intestine absorption of butyrate of ammonia produces the increased excretion of urea, acetone, and urinary volume. All the effects here observed, no doubt, are referable to the chemical nature of the employed salt and the way of introduction.

These premises well established, the question which now arises in the mind is whether or not in the common conditions of human life the intestinal putrefaction which constantly occurs from birth to death does or does not produce more or less abundant quantities of ammonia and volatile fatty acids, whose reabsorption would produce he formation of urea and acetone of putrefactive or extraphysiological origin. Before describing the method I have employed to verify the production and absorption of remarkable amounts of amoniacal salts of volatile fatty acids, it may be well to give a short exposition upon the nature and intensity of the chemical and bacterial phenomena which occur in the large intestine.

The intestinal flora which grows in the intestinal contents unfolds there with such a colossal development that more than 25 per cent. of the total organic matter of the feces are composed of bacterial residue. This intense bacterial life renovates incessantly. On the one hand the foodstuffs and the various excretions from the body through the gastro-intestinal tract bring the necessary aliment to its growth, and on the other the defensive forces of the intestinal mucous membrane and the noxious or antagonistic influences that certain groups of bacteria exercise upon others check this development. These conditions explain how a large proportion of dead bacterial matter may be excreted with the feces every twenty-four hours, as the fact has been evidenced by the Schmidt-Strasburger weight method: 5.3 grams of pure bacterial residue, or more than one hundred billions bacteria (calculated as Bacillus coli commune), are excreted daily.

In the small and large intestines the bacterial life exhibits great differences. While the small intestinal contents suffer the acid fermentation of the carbohydrates, it is five times more richer in water and travels with twenty-five times more rapidity than the large intestinal contents, a true normal fecal stasis taking place in the last portions of the alimentary canal. The matter becomes more and more poor in water and oxygen as a consequence of the absorption and powerful albuminous putrefaction, which commonly give it the alkaline reaction on account of the production of ammonia.

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[8] Palacios, Loc cit.

The intestinal contents have been studied chemically by various physiologists. Edwald,[9] Baumann,[10] MacFadyen, Nencki and Sieber[11] and others have made particular researches in the human intestine. The chemical composition of the small and large intestines differs in the same way as the bacteriological and physiological conditions referred to. The intestinal contents, as it has been collected through an artificial anus established at the distal end of the ileum, presents the following characteristics as they were observed by the last three authors named: the reaction was constantly acid, owing to the presence of organic acids, and notably of acetic acid. Other acids that were present were lactic, paralactic, various fatty acids, succinic, and the biliary acids. The odor but rarely suggested the existence of putrefactive changes. Indol, skatol, and phenol could not be demonstrated. Leucin and tyrosin were not found. Alcohol could always be demonstrated. Of gases, carbon dioxide was observed, and also faint traces of hydrogen sulphide, while methylmercaptan was absent. All these products of fermentation, as well as those originating from the normal action of digestive ferments, are completely oxidized and utilized for nutritive purposes.

In the large intestine, on the contrary, appear various products of the true albuminous putrefaction. The normal products of the digestive and fermentative proteolysis suffer the putrefactive degradation, and the resulting end-products, entirely abnormal in its origin and physiological character, are in greatest part eliminated with the feces or absorbed. It seems to be the biological law that all these products are not assimilated nor in any way utilized by the organisms. They are by their own nature or origin noxious or have toxic properties, and the organism, principally through the agency of its great antitoxic or defensive organ, the liver, tend to convert them into harmless substances as completely as possible. The putrefactive bacteria act on the various constructive stones of proteins, the amino-acids, following certain general chemical processes. The tryptophane or indol-amino-propionic acid, by the action of anaërobic bacteria, loses its amino (NH_2) group as NH_3. After this has been done other bacteria, endowed with some aërobic character, oxidize the remaining side chains, yielding carbonic acid and water. The residual indol or skatol is absorbed into the blood and reappears in the urine as indoxyl or skatoxyl in combination with sulphuric acid and alkalies as conjugated sulphates. The relative proportions in which these heterocyclic compounds appear in the urine depend upon the class of acting bacteria. According to Herter the Bacillus coli commune can produce indol under certain conditions and traces of skatol, while certain putrefactive bacteria produce this last substance in great abundance. According to the same author the indolacetic acid, another putrefactive or degradation product of tryptophane, is the chromogen of urorosein. Staal, Grosser, Porcher, and Hervieux believe that red skatol and urorosein are identical. Reasoning along these lines it is conceivable that, corresponding to a more remarkable change in the intestinal bacterial flora, other coloring matters may appear in the urine, as this has been observed, as a matter of fact, in the tropical and Atlantic region, where urorosein is replaced by cholerythrin.[12] Analogous transformations take place with other split products of protein. The tyrosin and phenylalanin, after having been desamided by the action of putrefactive bacteria losing ammonia, give various aromatic acids, phenol and cresol, and a small proportion of polyphenols. All these products are eliminated in the urine in the native state or in combination with sulphuric acid, glycocol or other compounds. Finally, leucin, butalanin, alanin, glycocol, asparaginic acid, glutaminic acid, and other non-aromatic amino-acids lose equally ammonia, and give rise in the intestine to various volatile fatty acids, such as capronic, valerianic, butyric, propionic, acetic, succinic, and glutaric acids. A certain part of these absorbed fatty acids may appear in the urine, increasing its amount of volatile acids only when they are absorbed in combination with the calcium, as the fact has been experimentally established.[13] Otherwise they are oxidized and destroyed. The butyric acid, which may be considered as an anaërobic and putrefactive product of the fatty amino-acids, and certain of its superior homologous derivatives yield acetone when they pass through the liver in combination with the ammonium, as the fact has been also established experimentally.

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[9] Ueber das Verhalten des Fistelsekretes, etc. Virchow's Archiv, vol. lxxv.

[10] Die aromatischen Verbindunges im Harn und die Darmfäulniss, Zeitschr. f. physiol. Chem., vol. x.

[11] Ueber die chem. Vorgänge im menschl. Dünndarm, Arch. f. exp. Path. u. Pharm., vol. xxviii.

As has been summarily explained above, the production of putrefactive ammonia is a phenomenon of universal occurrence in the human large intestine. It is closely related to the formation of other putrefactive products, which are also absorbed into the blood, transformed by the liver, and excreted in the urine. As a matter of fact the presence of ammonia in the large intestinal contents has been verified by all investigators after the first Brauneck[14] researches. Therefore it is a reasonable and scientific hypothesis, in accordance with all our knowledge upon physiological and chemical phenomena, this reabsorption of putrefactive ammonia and its transformation into urea. If the formation of putrefactive urea really occurs in the common conditions of life, it must be accompanied by the production and excretion in the urine of a corresponding amount of acetone, the two substances originating from the same biochemical transformation, as the above experiment suggests. The two phenomena are, however, by no means indissoluble, because other ammoniacal salts of putrefactive origin may be transformed into urea without the production of acetone, such as acetate or propionate of ammonia, and others.

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[12] Delgado Palacios, G., Why Yellow Fever is Endemic in the Tropical and Atlantic Region, Medical Record, July 25, 1914.

[13] Palacios, loc. cit.

[14] Brauneck, Mitteilungen aus der med. Klinik zu Würzburg, vol. ii.

The quantitative estimation of ammonia in the feces has been rarely performed. Schmidt and Strasburger[15] in their fundamental work upon chemical and bacteriological composition of human feces do not mention any quantitative estimation of this substance. This may be explained by the fact that the intestinal ammonia is generally considered as an obliged phenomenon of the intestinal putrefaction without importance and intended to be eliminated in the feces. I have made quantitative estimations of fecal ammonia on many occasions. I shall only quote here those estimations which I have performed with the purpose of establishing the reabsorption of ammonia in the large intestine. The estimations have been made by two methods at the same time, the formol titration and the Krüger-Reich-Schittenhelm method. The figures obtained by the two methods are nearly equal in every case, and therefore may be accepted as reliable. The following table shows the amounts of ammonia and volatile acids obtained in those persons who were submitted to the comparative experiment:

Names.	Feces weight. gm.	Ammonia. gm.	Volatile acids n/10. c.c.
A. C.	85.5	0.0756	89.8
L. E.	144.2	0.1485	81.3
B. de T. . . .	121.2	0.1108	139.7
P. A.	90.6	0.0539	60.8
R.	169.2	0.1900	100.3

The method I have employed to establish that ammoniacal salts of volatile fatty acids of putrefactive origin are effectively absorbed in the large intestine is founded upon the action of saline and drastic purgatives. It is well known that the first ones are absorbed in the stomach and first portion of the small intestine and afterward are excreted through the large intestinal mucous membrane. The second class of purgatives pass along the gastro-intestinal canal and appear to operate more especially by a mechanical and irritative action. The special precaution has been taken to receive into ice the watery evacuations so as to prevent the ulterior putrefactive fermentation. The following table shows the results obtained in the same persons by the use of saline purgatives:

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[15] Die Fäzes des Menschen, Berlin, 1910, p. 228.

Names.	Feces weight. gm.	Ammonia. gm.	Volatile acids n 10. c.c.
A. C.	933.4	0.1433	215.6
L. E.	881.9	0.1734	
B. de T.	1038.4	0.2124	252.4
P. A.	431.0	0.1223	155.6
R.	1213.5	0.2734	290.1

The drastic purgatives have produced a more pronounced action in the same individuals:

Names.	Feces weight. gm.	Ammonia. gm.	Volatile acids n 10. c.c.
B. de T.	514.9	0.3167	452.0
P. A.	529.0	0.1521	184.3
R.	898.3	0.3107	552.0

These experimental researches prove evidently that there is present in the large intestine, in a given moment or during a certain time, a greater amount of ammonia and volatile fatty acids than the quantity which goes out with the feces every twenty-four hours. The differences reach easily 100 milligrams and more; and it is greater for the fatty acids.

Although these figures are quite remarkable, there are many reasons to believe that they are really greater. The production and absorption of fecal ammonia are continual and concomitant phenomena. When the intestinal contents pass the Bauhin valve and enter the large intestine the matter suffers the ammoniacal putrefaction and is five times more rich in water than when it goes out. The purgative surprises the matter as it is contained in the large intestine, in a given moment, and carries it away. Hence it is easy to infer that the drastic evacuation, although less rich in water and weight, contains a greater proportion of ammonia than the saline evacuation, as the reported figures demonstrate. The ammonia which is violently expelled through the agency of the purgatives corresponds to the ammonia produced during the time of their action, eight hours more or less, that is to say, three times smaller than the twenty-four hours' produced ammonia. And this evaluation manifestly represents a minimum, because very probably the purgative action interferes with the ammoniacal putrefaction, and the production of this substance is less pronounced than when the matter is quietly left to its anaërobic stagnation and putrefaction. The amount which is quantitative estimated in the feces represents only the residue which has not been absorbed. The difference between the two quantities corresponds to the amount which would be absorbed, in the supposition that the purgative would not have interfered with the intestinal putrefaction, and that normal conditions of the intestinal contents would have been the same.

In the purgative evacuations from mellitus or insipidus diabetics I have determined a greater quantity of ammonia than in the normal condition. The amount of volatile fatty acids by the same method reach enormous figures in the same diseases. In these patients a greater proportion of volatile fatty acids has been also verified in the urine. I cannot explain in detail why, in these patients, the volatile fatty acids increase in so large amounts in the urine, while they do not augment above the normal when they are introduced directly into the rectum in combination with the ammonium as in the experiment refered to. I can only say that this depends upon their combination with the calcium, and that I have obtained experimentally this augmentation.[16]

The fecal reabsorption of volatile fatty acids is a known and admitted fact for a long time, and has been verified in man by the same direct method, that is, the action of drastic purgatives. Schmidt and Strasburger[17] says: "In the same person it has been possible to establish that during a three days' constipation (through voluntary checking of the urging to stool) the amounts of volatile fatty acids diminish in the feces, while the quantity of the same acids in castor-oil evacuations becomes three times larger. The observed difference proceeds evidently from quantitative changes of the fecal reabsorption." On the other hand, H. Strauss and H. Philippsohn,[18] by means of their method of estimating volatile fatty acids in the urine, have obtained the highest value in constipation comparatively with the normal condition.

The conclusion may be drawn, from the above experiments and those of other investigators, that it is scientifically correct to establish that, in the common conditions of human life and in normal subjects, a minimum of 300 mg. of ammonia is produced every twenty-four hours in the large intestine as a result of putrefactive processes; in some cases this quantity has amounted to twice as much (case B. de T.); and that this ammonia, after having been absorbed into the blood, appears in the urine as a minimum of 0.5 gram and even 1 gram of putrefactive urea. To this daily amount of putrefactive urea corresponds normally the production of several milligrams of acetone.

I cannot enter, in the present article, into all the details that this great question of putrefactive urea requires to be scientifically criticised and to be put in accord with all admitted physiological and pathological facts. I can only say that the phenomenon of putrefactive urea is not in contradiction with our knowledge on nutrition researches. The fact may have passed unnoticed even in the most strict nutritive balances. The comparison between the three values, fecal nitrogen, urinary nitrogen, and alimentary nitrogen, may have been realized without the putrefactive urea phenomenon being disclosed.

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[16] Palacios, loc. cit.

[17] Loc. cit.

[18] Neubauer-Huppert, Analyse des Harns, Wiesbaden, 1910, p. 190.

The production of acetone in the animal body is a question which actually is too far from its definitive solution. The experimental researches of Embden and his collaborators closely relates this production to butyric acid and some other simple compounds. But from what classes of substances or processes this butyric acid or compounds proceed is not known at present. Various physiologists believe that the destruction of proteins is the principal source of acetone; others attribute their origin to fat destruction. A well-observed fact is the counteraction of carbohydrares upon the production of acetone (anticetoplastic action) and also the constant increase of this substance in man during fast. The scientific criticism of all these questions would lengthen the present article beyond its proper scope; but all these facts and hypotheses may find, in the production of putrefactive acetone, a new and satisfactory explanation. The production of a small amount of acetone in the normal state, intimately related with the production of a certain amount of putrefactive urea, can receive from this conception an entirely more satisfactory explanation than its doubtful and obscure nutritive origin.

I hope the present ideas, founded on experiments carried out on man and corresponding to the common conditions of human life, will be of great importance to physiology and pathology. It would be also very satisfactory to the author to have laboratory men confirm the described experiments.